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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	**PAPER NUMBER**
1635	

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13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/873,546	Clark
Examiner	**Art Unit**
Richard Schnizer	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 4, 2003* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above, claim(s) *5 and 17-28* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-4 and 6-16* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Jan 7, 2002* is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 9
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

An information disclosure statement was received and entered as Paper No. 9 on 7/22/02.

A response to restriction requirement was received and entered as Paper No. 12 on 3/4/03. Applicants election with traverse of group 1, claims 1-4 and 6-16 drawn to drawn nucleic acids encoding the amino acid sequence of SEQ ID NO: 5 is acknowledged. Traversal is on the grounds that there would be no undue burden in additionally searching claims 21-28 because art uncovered in the search of these claims would be relevant to the search of claims 1-4 and 6-16. This is unpersuasive because the elected group contains claims directed to methods of detecting nucleic acids in a sample, as recited in claims 6-10, and methods of amplifying nucleic acids as recited in claims 11-16, and a search of methods of inhibiting cell growth recited in claims 21-28 would not be coextensive with the subject matter of claims 6-16. Because the searches of the elected and nonelected inventions would be non-coextensive, and because the inventions are independent and distinct for the reasons set forth in the restriction, searching all the claims would cause an undue burden on the Examiner. For these reasons the restriction requirement is deemed proper and is made FINAL.

Claims 5 and 17-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 12.

Claims 1-4 and 6-16 are under consideration in this Office Action.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. See e.g. page 44, line 3.

Claim Objections

Claims 11-16 are objected to because they contain the acronym "PCR". Applicant should amend the first claim containing the acronym to contain the full name of what is implied by the acronym followed by the acronym in parentheses, e.g. "polymerase chain reaction (PCR)", as in the specification at page 18, lines 6-8.

Compliance with Sequence Rules

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reason(s). This application clearly fails to comply with the requirements of 37 C.F.R.1.821-1.825. Applicant's attention is directed to the final rule making notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998). **Figure 2 sets forth nucleotide sequences in excess of 10**

nucleotides, but these sequences are not identified by a SEQ ID NO in either the Figure or the Brief Description of Figures. It appears that these sequences probably correspond to SEQ ID NOS 4 and 9-15 in the current Sequence Listing. If this is the case, then Applicant should simply amend the Figures or Brief Description of Figures to recite the appropriate SEQ ID NOS. If these of sequences are not disclosed in the current Sequence Listing then Applicant must provide:

A substitute computer readable form (CRF) copy of the "Sequence Listing";

A substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification;

and

A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216

For CRF Submission Help, call (703) 308-4212

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Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 6-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of detecting by hybridization and subsequent nucleic acid sequencing nucleic acids encoding the polypeptide of SEQ ID NO:5, does not reasonably provide enablement for methods of detecting or amplifying nucleic acids encoding a "Rig" polypeptide other than SEQ ID NO:5. Further, the specification does not reasonably provide enablement for methods of using 2 oligonucleotides to amplify nucleic acids encoding Rig when both oligonucleotides are complementary to portions of SEQ ID NO:4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 6-10 are drawn to methods of detecting nucleic acids encoding "Rig" in a sample by detecting a hybridization complex between a probe having complementarity to at least a portion of SEQ ID NO:4 and a nucleic acid. Claims 11-16 are drawn to methods of amplifying by PCR a nucleic acid encoding Rig using "two oligonucleotides having complementarity to SEQ ID NO:4." The specification teaches that, in one embodiment, Rig is encoded by SEQ ID NO:4 and has the amino acid sequence of SEQ ID NO:5 (see page 5, lines 5-8).

The scope of the claimed invention is unclear because the specification fails to give an adequate definition of what is, and is not, a Rig polypeptide. The specification provides guidance as to the function of the version of Rig that is SEQ ID NO:5. This protein is expressed in fetal and adult brain and heart, but not in a variety of other tissues. Expression is reduced or zero in some tumor derived neuronal cell lines and tumor-derived tissue samples, but appears normal in others (see e.g. Fig. 12, lanes 3, 4, 6, and 9-12). Constitutive expression of SEQ ID NO:4 inhibits focus formation in NIH 3T3 cells. The protein antagonizes Ras-dependent Elk-1 transcription factor activity, and inhibits the growth of U251 and A673 neuronal tumor-derived cells when expressed ectopically in these lines. An S21N mutation of SEQ ID NO:5 (analogous to Ras S17N) causes transformation when expressed in NIH 3T3 cells. Finally, Rig coprecipitates with Raf-1, a kinase which is regulated by H-Ras and K-Ras. However, the specification fails to teach what are the minimum sequence and functional characteristics a given polypeptide must have in order to be recognized as a Rig polypeptide. For example, the specification teaches that Noey2 is a related polypeptide (63% identity, see page 44, lines 24-29) that is similar to Rig inasmuch as it is a G-protein and appears to be a tumor suppressor, but it is unclear if Noey2 falls within the genus of Rig polypeptides. An alignment between the Noey2 polynucleotide sequence and SEQ ID NO:4 shows that there is a segment of 81% identity from position 307-364 of SEQ ID NO:4 (see attached alignment). So, while it is clear that this fragment of SEQ ID NO:4 could be used to identify Noey2 by hybridization, it is unclear if Noey2 falls within the claimed genus because the specification fails to adequately define what is a Rig polypeptide.

Even if the specification did define what functional attributes are required to qualify a polypeptide as a Rig polypeptide, it would fail to adequately enable the invention because neither it nor the prior art teaches the required structural limitations for Rig polypeptides, and one of skill in the art could not determine these without undue experimentation.

At the time the invention was filed the Ras protein superfamily contained about 150 members which functioned to transduce a wide variety of signals in cells. See Paduck et al (Acta Biochemica Polonica 48(4): 829-850, 2001) page 830, column 1, first line of last paragraph. These proteins all comprise a guanine nucleotide binding domain with a high affinity for GTP or GDP, and low (but extremely variable within the superfamily) catalytic activity. The nucleotide binding site also contributes to the binding of effector molecules which are activated by Ras and which mediate the wide variety of cellular responses. The phosphorylation state of the nucleotide in the binding site regulates the activity of the Ras protein, (GDP activates Ras, and GTP inactivates Ras), and influences recognition and binding of effector molecules. So, structural differences between Ras molecules govern the rate at which GTP is hydrolyzed as well as the identity of effector molecules with which they interact, and consequently the nature of signals that are transduced. See page 833, column 1, last full paragraph of Paduck. Although various Ras nucleotide binding sites are well known and highly conserved, it is unclear what governs the substantial kinetic differences in GTP/GDP exchange observed in the various Ras proteins. See last sentence of paragraph bridging columns 1 and 2 on page 833 of Paduck.

Generally speaking, the effects of amino acid substitutions on polypeptide activity are unpredictable. While it is known that many amino acid substitutions are generally possible in any given protein, certain positions in a polypeptide sequence are critical to the protein's structure/function relationship, such as various sites or regions where the biological activity resides or regions directly involved in binding, stability or catalysis, or which provide the correct three-dimensional spatial orientation for biologically active binding sites, or which represent other properties or characteristics or properties of the protein. These or other regions may also be critical determinants of activity. These regions can tolerate only relatively conservative substitutions, or no substitutions. See Bowie et al (1990). The prior art teaches that the effects of amino acid substitutions and deletions on protein function were highly unpredictable. Rudinger (In Peptide Hormones J.A. Parsons, Ed. University Park Press, Baltimore, 1976, page 6) teaches that "[t]he significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study." Furthermore Ngo et al (In The Protein Folding Problem and Tertiary Structure Prediction, K. Merz Jr. and S. Legrand, Eds. Birkhauser, Boston, 1994, see page 492) teaches that "[i]t is not known if there exists an efficient algorithm for predicting the structure of a given protein from its amino acid sequence alone. Decades of research have failed to produce such an algorithm". In the specific case of Ras proteins, Paduck teaches that the effects on the activity of the protein of mutations in the nucleotide binding site are unpredictable. Furthermore, site directed mutagenesis studies have shown that mutations affecting nucleotide binding, and

therefore signal transduction, are not limited only to the nucleotide binding site, but are found in segments well outside the nucleotide binding site. See paragraph bridging columns 1 and 2 on page 834. Because neither the prior art nor the specification provides adequate guidance as to how to generally predict the effects of amino acid substitutions within even the highly conserved nucleotide binding site of Ras proteins, and because the specification fails to teach what are the structural limitations that define Rig polypeptides, one of skill in the art could not determine without undue experimentation what sequences other than SEQ ID NO:5 are Rig polypeptides, and could not practice methods of identifying or amplifying nucleic acids encoding Rig polypeptides other than SEQ ID NO:5. One might argue that it would not be undue experimentation to express and assay polypeptides individually using the assays taught in the specification, and thereby empirically determine the function of each one. However as set forth in *In Re Fisher*, 166 USPQ 18(CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and **their performance characteristics predicted by resort to known scientific laws**; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with the degree of unpredictability of the factors involved.

Emphasis added. The specification fails to provide any theoretical framework which can be used to accurately predict which amino acid substitutions will adequately maintain Rig structure and function. In the absence of such guidance, one of skill in the art would have to perform undue experimentation in order to make the invention commensurate in scope with the claims.

The following section pertains directly to claims 11-16 which lack enablement because they require that each of two oligonucleotide primers in a method of amplifying Rig polynucleotides must be complementary to SEQ ID NO:4. The invention as claimed in inoperable.

The state of the art of primer-mediated nucleic acid amplification was set forth by Mullis et al (US Patent 4,965,188, issued 10/23/90) who taught that, in order to amplify a nucleotide sequence, two primers were required: one complementary to the sequence to be amplified, and the other identical to a portion of the sequence to be amplified. In other words, to amplify a double stranded nucleic acid, one needs to anneal primers to each complementary strand. The invention as claimed would result in annealing of primers to only one strand: SEQ ID NO:4.

The specification fails to teach any primers complementary to SEQ ID NO:4 that can be used, in tandem, to amplify any nucleic acid encoding Rig. While Applicant is not required to disclose that which is well known in the art, there is an obligation to disclose critical elements of the invention as well as how to use these elements. In Genentech, Inc, v Novo Nordisk A/S, the court found that when the specification omits any specific starting material required to practice an invention, or the conditions under which a process can be carried out, there is a failure to meet the enablement requirement. See 42 USPQ2d 1001.

> It is true, as Genentech argues, that a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement

> that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

In this case, the identification of two oligonucleotide sequences complementary to SEQ ID NO:4 that can be used to amplify a nucleic acid encoding Rig cannot be considered a minor detail which can be omitted in the process of providing an enabling disclosure.

In summary, because the specification fails to adequately teach what is encompassed by the term "Rig", and fails to teach what are the structural and functional limitations of Rig polypeptides, one of skill in the art could not identify or amplify a nucleic acid encoding a Rig polypeptide, other than SEQ ID NO:5, without undue experimentation. Further, claims 11-16 lack enablement because the specification does not teach how to perform oligonucleotide primer mediated amplification using two primers that are complementary to the same strand of nucleic acid (SEQ ID NO:4).

Written Description

Claims 6-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 6-10 are drawn to methods of identifying species of the genus of polynucleotides encoding a Rig polypeptide. The species must be capable of hybridization with a probe having

complementarity to at least a portion of SEQ ID NO:4. Claims 11-16 are drawn to methods of amplifying and identifying species of the genus of polynucleotides encoding a Rig polypeptide. The polynucleotides must have complementarity to at least a portion of SEQ ID NO:4.

As noted above under enablement, the scope of the claimed genuses is unclear because the specification fails to give an adequate definition of what is, and is not, a Rig polypeptide. The specification discloses the sequences of 8 Ras-related polypeptides, in addition to the sequence of Rig, but it is not clear whether or not these polypeptides are intended to be within the scope of the invention, because the specification fails to teach what are the minimum sequence and functional characteristics a given polypeptide must have in order to be recognized as a Rig polypeptide. Furthermore, the claims recite no functional requirements and only limited structural requirements. Claim 16 is the narrowest claim because it requires that the primers used for amplifying genes must comprise SEQ ID NOS: 2 and 3, which are designed to amplify double stranded polynucleotides comprising SEQ ID NO:4. However, claims 6-16 require only partial complementarity of the recited probes or primers to SEQ ID NO:4. So, these claims embrace probes and primers that have large regions of non-complementarity to SEQ ID NO:4, and that can detect or amplify sequences that have little or no relationship to SEQ ID NO:4. Because the claims recite no functional limitations regarding the activity of the encoded polypeptide, the scope of the claimed genus is unclear and one of skill in the art could not conclude that Applicant was or was not in possession of the claimed genus at the time of filing.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4 and 6-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-4 and 6-16 are indefinite because it is unclear what is intended by "Rig". The specification fails to give this term a limiting definition, and one of skill in the art cannot know the metes and bounds of the claims. For example it is unclear what are the minimum sequence and function characteristics a given polypeptide or polynucleotide must have in order to be defined as a "Rig" polypeptide or polynucleotide.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Lamerdin et al (GenBank Accession No. AC006538, published 2/7/1999).

Lamerdin et al teach a bacterial artificial chromosome comprising 177 kb of human chromosome 19, including a segment encoding the amino acid sequence of SEQ ID NO: 5. See attached sequence and alignment. Because the artificial chromosome comprises 105 kb of contiguous genomic sequence upstream of the start codon of the sequence encoding SEQ ID NO:5, it is clear that this nucleic acid comprises the transcriptional control elements for this open reading frame. For this reason, the bacterial artificial chromosome of Lamerdin is an expression vector for SEQ ID NO:5. Because bacterial artificial chromosomes are replicated and maintained in bacteria, the disclosure of Lamerdin anticipates claim 4, requiring a prokaryotic host cell.

Thus Lamerdin anticipates the claims.

Claims 6-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Yu et al (Proc. Nat. Acad. Sci. USA 96: 214-219, 1999).

Yu teaches detection by Northern blot analysis of polyA RNA from human tumor tissue of a nucleic acid that encodes a polypeptide 63% identical to SEQ ID NO:5. See page 214, column 2, first full paragraph; paragraph bridging pages 215 and 216; and instant specification at page 43, lines 25-29 and page 4, lines 24-29. The probe was a set of random primed fragments of a NOEY2 cDNA. Yu also teaches identification of a Noey2 gene in genomic DNA *in situ* by hybridization with a nucleic acid containing Noey2. See Fig. 4 on page 217. As discussed above

under 35 112, first paragraph rejections, Noey2 DNA has regions of complementarity to SEQ ID NO:4. Because Noey2 nucleic acids were identified probes with complementarity to at least part of SEQ ID NO:4, and because the specification does not exclude Noey2 from the genus of polypeptides that may be construed as Rig polypeptides, these methods of Yu anticipate claims 6-10.

The amplification methods of claims 11-15 require two oligonucleotides having complementarity to SEQ ID NO:4. However, the claims do not recite any minimum amount of complementarity required, so Rig amplification methods using oligonucleotides having only a single base in common with SEQ ID NO:4 could anticipate the claims. Because SEQ ID NO:4 contains all four deoxynculeotide bases, any Rig amplification method using DNA primers could anticipate the claims. Yu teaches several methods of DNA oligonucleotide primer-mediated PCR amplification and detection of nucleic acids encoding Noey2. See e.g. first, second, fourth, and fifth full paragraphs of column 1 on page 215. Thus Yu anticipates these claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 and 2 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lamerdin et al (GenBank Accession No. AC006538, published 2/7/1999).

Lamerdin et al teach a bacterial artificial chromosome comprising 177 kb of human chromosome 19, including a segment encoding the amino acid sequence of SEQ ID NO: 5. See attached sequence and alignment. The nucleotide sequence of Lamerdin differs from SEQ ID NO:4 by a single, silent base change in a glutamine codon at a position corresponding to position 70 of SEQ ID NO:5. The codon in SEQ ID NO:4 is CAA, whereas the codon reported by Lamerdin et al is CAG. Because CAA and CAG codons both encode glutamine, they are art-recognized equivalents. MPEP 2144.06 indicates that it is obvious to substitute for one another components that are known in the prior art to have equivalent characteristics in the claimed environment. Furthermore, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Hence it would have been prima facie obvious to one of ordinary skill in the art to substitute the sequence of Lamerdin for that of SEQ ID NO:4.

Thus the invention as a whole was *prima facie* obvious.

Claims 1, 3 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lamerdin et al (GenBank Accession No. AC006538, published 2/7/1999), in view of Kimmelman et al (Oncogene (1997) 15(22): 2675-2685), Der et al (US Patent 6,077,686, issued 6/20/2000), and Baker et al (Nucl. Acids. Res. (1997) 25(10): 1950-1956).

Lamerdin et al teach a bacterial artificial chromosome comprising 177 kb of human chromosome 19, including a segment encoding the amino acid sequence of SEQ ID NO: 5. See attached sequence and alignment. Lamerdin teaches that the sequence encodes a protein similar to RAS-related proteins.

Lamerdin does not teach a vector comprising a replication defective virus, or a eukaryotic host cell.

Kimmelman teaches the cloning of a RAS-related gene, its transfer to a plasmid expression vector, and analysis of expression of the encoded protein in eukaryotic cells. See abstract, Fig. 2, panel b, Fig. 4 on page 2679 on page 2677, and Fig. 7, panel a on page 2681.

Der et al teach that expression vectors comprising plasmids or replication defective viruses are functional equivalents. See column 11, lines 58-67.

Baker teaches that transfection efficiency of bacterial artificial chromosomes to eukaryotic cells is inefficient. See abstract.

It would have been obvious to one of ordinary skill in the art at the time of the invention to transfer the RAS-related open reading frame of Lamerdin to a plasmid or replication-defective virus. One would have been motivated to do so in order to facilitate analysis of the gene and its product because members of the Ras subfamily have been shown to be involved in signal transduction and tumorigenesis, and because determining the function of RAS-related genes is an important step in understanding the complexity of intracellular signaling. See e.g. Kimmelman abstract and page 2676, column 1, last paragraph prior to Results. One of ordinary skill in the art

recognizes that transfer of the sequence from a 177 kb artificial chromosome to a different expression vector such as a plasmid or replication deficient virus would facilitate analysis of the gene, because higher transfection efficiency can be achieved with these vectors (see Baker above). MPEP 2144.06 indicates that it is obvious to substitute for one another components that are known in the prior art to have equivalent characteristics in the claimed environment. Furthermore, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). In this case Der teaches that plasmids and replication defective viruses may be used interchangeably as expression vectors, thus these are art-recognized equivalent components in the context of gene expression, and it would have been prima facie obvious to one of ordinary skill in the art to use either type of vector for the expression and analysis of the sequence of Lamerdin. On the other hand one could have improved the transfection efficiency of the baculovirus clone of Lamerdin by adding to it psoralen-inactivated adenovirus as taught by Baker. Because the adenovirus of Baker is inactivated, it is considered to be replication deficient, thereby meeting the limitations of claim 3.

Thus the invention as a whole was *prima facie* obvious.

Claims 1, 6-11 and 13-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lamerdin et al (GenBank Accession No. AC006538, published 2/7/1999) in view of Kimmelman et al (Oncogene (1997) 15(22): 2675-2685).

Lamerdin et al teach a bacterial artificial chromosome comprising 177 kb of human chromosome 19, including a segment encoding the amino acid sequence of SEQ ID NO: 5. See attached sequence and alignment. Lamerdin teaches that the sequence encodes a protein similar to RAS-related proteins.

Lamerdin does not teach a method of detecting in a sample nucleic acids by Northern blot using a probe having complementarity to a portion of the nucleotide sequence of SEQ ID NO:4, or a method of amplifying nucleic acids by using PCR primers for amplifying SEQ ID NO:4.

Kimmelman teaches the cloning of a RAS-related gene by PCR amplification, transfer of the gene to a plasmid expression vector, analysis of expression of the encoded protein in eukaryotic cells, and methods of detecting the corresponding mRNA in a variety of human tissues by Northern blot of total cellular RNA. See abstract, Fig. 2, panel b, Fig. 4 on page 2679 on page 2677, and Fig. 7, panel a on page 2681. It is noted that total cellular RNA comprises polyA RNA.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the Northern blot method of Kimmelman to detect nucleic acids encoding SEQ ID NO:5 in human tissues, including tumor tissues, using a probe comprising at least a portion of SEQ ID NO:4. One would have been motivated to do so because it is apparent from the teachings of Kimmelman that determining the pattern of expression of newly discovered RAS-related genes is essential to understanding their function, and because Kimmelman teaches that RAS-related genes are involved in tumorigenesis and are therefore of biomedical interest. See abstract, page 2676, column 1, last paragraph prior to Results, and paragraph bridging pages 2680 and 2681.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use PCR amplification to transfer the sequence of Lamerdin from the bacterial artificial chromosome to an expression vector as taught by Kimmelman. See page 2682, column 2, lines 1-10 of paragraph bridging pages 2682 and 2683. One would have been motivated to do so because PCR allows one to insert restriction enzymes of choice onto the termini of a given open reading frame, as evidenced by Kimmelman who used PCR primers containing BamHI or EcoRI sites, thereby facilitating insertion into a vector of choice in an orientation of choice.

Thus the invention as a whole was *prima facie* obvious.

Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lamerdin et al (GenBank Accession No. AC006538, published 2/7/1999) and Kimmelman et al (Oncogene (1997) 15(22): 2675-2685) as applied to claims 1, 6-11 and 13-15 above, and further in view of Mullis et al (US Patent 4,965,188, issued 10/23/90), and Takarada (US patent 5,981,183, issued 11/9/99).

Lamerdin et al teach a bacterial artificial chromosome comprising 177 kb of human chromosome 19, including a segment encoding the amino acid sequence of SEQ ID NO: 5. See attached sequence and alignment. Lamerdin teaches that the sequence encodes a protein similar to RAS-related proteins. Kimmelman teaches the cloning of a RAS-related gene by PCR amplification, transfer of the gene to a plasmid expression vector, analysis of expression of the encoded protein in eukaryotic cells, and detection of the corresponding mRNA in a variety of

human tissues. See abstract, Fig. 2, panel b, Fig. 4 on page 2679 on page 2677, and Fig. 7, panel a on page 2681.

These references do not explicitly teach a DNA polymerase comprising both DNA-dependent DNA polymerase activity and RNA-dependent DNA polymerase activity.

Mullis teaches amplification of DNA sequences by polymerase chain reaction (PCR), using DNA polymerase from *Thermus aquaticus*. See *e.g.* claim 5.

Takarada teaches that DNA polymerase from *Thermus aquaticus* comprises both DNA dependent DNA polymerase activity and RNA dependent DNA polymerase activity. See column 9, lines 62-67.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the *Thermus aquaticus* DNA polymerase of Mullis to amplify the sequence of Lamerdin as taught by Kimmelman. One would have been motivated to do so because *Thermus aquaticus* DNA polymerase is stable at the high temperatures required for denaturation in PCR. See abstract of Mullis. The limitations of claim 12 are met because *Thermus aquaticus* DNA polymerase inherently comprises both DNA dependent DNA polymerase activity and RNA dependent DNA polymerase activity. See Takarada.

Thus the invention as a whole was *prima facie* obvious.

Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lamerdin et al (GenBank Accession No. AC006538, published 2/7/1999) and Kimmelman et al (Oncogene

(1997) 15(22): 2675-2685) as applied to claims 1, 6-11 and 13-15 above, and further in view of Mullis et al (US Patent 4,965,188, issued 10/23/90).

Lamerdin et al teach a bacterial artificial chromosome comprising 177 kb of human chromosome 19, including a segment encoding the amino acid sequence of SEQ ID NO: 5. See attached sequence and alignment. Lamerdin teaches that the sequence encodes a protein similar to RAS-related proteins. Kimmelman teaches the cloning of a RAS-related gene by PCR amplification, transfer of the gene to a plasmid expression vector, analysis of expression of the encoded protein in eukaryotic cells, and detection of the corresponding mRNA in a variety of human tissues. See abstract, Fig. 2, panel b, Fig. 4 on page 2679 on page 2677, and Fig. 7, panel a on page 2681.

These references do not explicitly teach a method of amplifying RNA, as recited in claim 15.

Mullis teaches that PCR amplification of messenger RNA sequences allows an improvement in detection of target sequences without the use of radioactive labels. See column 7, lines 16-24 and paragraph bridging columns 19 and 20.

It would have been obvious to one of ordinary skill in the art at the time of the invention amplify mRNA sequences by PCR in order to characterize the pattern of tissues in which the sequence of Lamerdin was expressed, rather than Northern blotting as taught by Kimmelman. One would have been motivated to do so because PCR allows greater sensitivity and would have obviated the need for the radioactive label use by Kimmelman.

Thus the invention as a whole was *prima facie* obvious.

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lamerdin et al (GenBank Accession No. AC006538, published 2/7/1999) and Kimmelman et al (Oncogene (1997) 15(22): 2675-2685) as applied to claims 1, 6-11 and 13-15 above, and further in view of Erlich et al (US Patent 5,314,809, issued 5/24/94) and DeBoer et al (US Patent 5,397,703, issued 3/14/95).

Lamerdin et al teach a bacterial artificial chromosome comprising 177 kb of human chromosome 19, including a segment encoding the amino acid sequence of SEQ ID NO: 5. See attached sequence and alignment. Lamerdin teaches that the sequence encodes a protein similar to RAS-related proteins. Kimmelman teaches the cloning of a RAS-related gene by PCR amplification, transfer of the gene to a plasmid expression vector, analysis of expression of the encoded protein in eukaryotic cells, and detection of the corresponding mRNA in a variety of human tissues. See abstract, Fig. 2, panel b, Fig. 4 on page 2679 on page 2677, and Fig. 7, panel a on page 2681.

Erlich teaches that PCR primers may be modified by the inclusion of G and or C residues at their 5' ends in order to improve thermostability. See column 3, lines 35-42.

DeBoer teaches the modification of PCR primers to include both a 5' C-G clamp and a restriction site. See column 14, lines 9-11.

These references do not teach a oligonucleotides comprising SEQ ID NOS:2 and 3.

It would have been obvious to one of ordinary skill in the art at the time of the invention to synthesize for PCR oligonucleotide primers comprising SEQ ID NOS:2 and 3. One would have been motivated to do so in order to transfer the sequence of Lamerdin from a bacterial artificial chromosome to a plasmid expression vector having a higher transfection efficiency. In order to amplify and transfer the sequence of Lamerdin, one would have chosen primers corresponding to the 5' and 3' ends of the ORF of Lamerdin, as in SEQ ID NOS: 2 and 3. Additionally one would have been motivated to include restriction sites 5' to the portions of the primers corresponding to the ORF, in order to facilitate cloning of the resulting PCR fragment. For example, Kimmelman teaches the incorporation of Bam HI and Eco RI sites, as are incorporated into instant SEQ ID NOS: 2 and 3, respectively. See lines 1-10 of paragraph bridging pages 2682 and 2683 of Kimmelman. Finally, it is routine in the art to add G and or C residues to the 5' ends of primers in order to increase the thermostability of the primers. This is apparent from the teachings of both Erlich and DeBoer. In fact DeBoer teaches the combination of restriction sites and G/C clamps at the 5' prime ends of PCR primers.

Thus the invention as a whole was *prima facie* obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441.

The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

DAVET NGUYEN
PRIMARY EXAMINER

Richard Schnizer, Ph.D.

1: AC006538. Homo sapiens chro...[gi:4235145]
LOCUS AC006538 177540 bp DNA linear PRI 07-FEB-1999
DEFINITION Homo sapiens chromosome 19, BAC 41195 (CIT-B-31c16), complete sequence.
ACCESSION AC006538
VERSION AC006538.1 GI:4235145
KEYWORDS HTG.
SOURCE Homo sapiens (human)
ORGANISM Homo sapiens
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE 1 (bases 1 to 177540)
AUTHORS Lamerdin,J.E., McCready,P.M., Skowronski,E., Viswanathan,V., Burkhart-Schultz,K., Gordon,L., Dias,J., Ramirez,M., Stilwagen,S., Phan,H., Velasco,N., Do,L., Regala,W., Terry,A., Garnes,J., Danganan,L., Erler,A., Christensen,M., Georgescu,A., Avila,J., Liu,S., Attix,C., Andreise,T., Trankheim,M., Amico-Keller,G., Coefield,J., Duarte,S., Lucas,S., Bruce,R., Thomas,P., Quan,G., Kronmiller,B., Arellano,A., Sanders,C., Ow,D., Nolan,M., Trong,S., Kobayashi,A., Olsen,A.S. and Carrano,A.V.
TITLE Sequence analysis ofa 3.5 Mb contig in human 19p13.3 containing a serine protease gene cluster
JOURNAL Unpublished
REFERENCE 2 (bases 1 to 177540)
AUTHORS Lamerdin,J.E.
TITLE Direct Submission
JOURNAL Submitted (07-FEB-1999) Joint Genome Institute, Lawrence Livermore National Laboratory, 7000 East Ave., Livermore, CA 94551, USA
COMMENT Map and sequence oriented from p telomere to centromere. BC41195 (CIT-B-31c16) is currently separated from cosmid R32203 (AC006275) to the left by a sequence gap of approximately 6 kb, and overlaps BAC 102889 (CIT-B-191n6; AC006130) to the right from bases 175,545 to 177,540. Additional map and sequence information are available at: http://www-bio.llnl.gov/bbrp/genome/genome.html.

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                     proteins; Hypothetical protein 64%
identical to
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by ORF C54A12.4
                     (U28733)"
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                     /evidence=not_experimental
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LIVQIKGSVEDIPVMLVGNKCDETQREVDTREAQAVAQEWKCAFMETSAKMNYNVKEL
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  Matches  596;  Conservative    0;  Mismatches    1;  Indels    0;  Gaps    0;

Qy       1 ATGCCGGAACAGAGTAACGATTACCGCGTGGTGGTGTTCGGGGCGGGCGGCGTGGGCAAG 60
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Qy      61 AGCTCGCTGGTGCTGCGCTTCGTGAAGGGCACGTTCCGCGACACCTACATCCCCACCATC 120
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Qy     181 GACACCACCGGCAGCCACCAGTTCCCGGCCATGCAGCGCCTGTCCATCTCCAAGGGCCAC 240
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Db   72826 GACACCACCGGCAGCCACCAGTTCCCGGCCATGCAGCGCCTGTCCATCTCCAAGGGCCAC 72767

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Qy     301 TACAAGCTCATCGTGCAGATCAAGGGCAGCGTGGAGGACATCCCCGTGATGCTCGTGGGC 360
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Qy     361 AACAAGTGCGATGAGACGCAGCGGGAGGTGGACACGCGCGAGGCGCAGGCGGTGGCCCAA 420
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Qy     481 TTCCAGGAGCTGCTGACGCTGGAGACGCGCCGGAACATGAGCCTCAACATCGACGGCAAG 540
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Qy     541 CGCTCCGGGAAGCAGAAGAGGACAGACCGCGTCAAGGGCAAATGCACCCTCATGTGA 597
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```

ALIGNMENT OF SEQ ID: 4 AND NOEY2

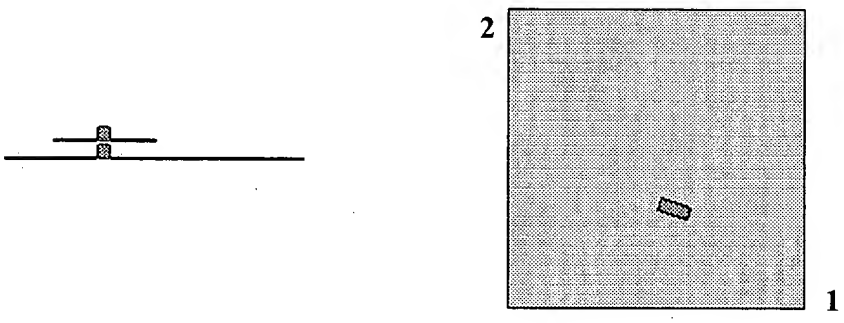
Blast 2 Sequences results

BLAST 2 SEQUENCES RESULTS VERSION BLASTN 2.2.5 [Nov-16-2002]

Match: 1 Mismatch: -2 gap open: 5 gap extension: 2
x_dropoff: 50 expect: 10.0 wordsize: 11 Filter ☑ Align

Sequence 1 lcl|seq_1 **Length** 597 (1 .. 597)

Sequence 2 gi 4100354 **Length** 1495 (1 .. 1495)



NOTE: The statistics (bitscore and expect value) is calculated based on the size of nr database

NOTE: If protein translation is reversed, please repeat the search with reverse strand of the query sequence

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Score = 48.8 bits (25), Expect = 0.010
Identities = 47/58 (81%)
 Strand = Plus / Minus
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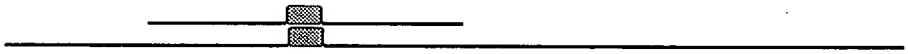

13 mer

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Query: 307 cagctcctccagcgactgcttgctggtgacggagaacaccaggatgaaggcgtggccc 364
          |||||| ||||| |  | |||  ||||||| ||| | ||||||| ||||||||||||
Sbjct: 529 cagctcttccagggtttccttcttggtgactgagtagaccaggacgaaggcgtggccc 472
NOEY2  109  L  E  E  L  T  E  K  K  T  V  S  Y  V  L  V  F  A  H  G

CPU time:      0.07 user secs.       0.04 sys. secs          0.11 total secs.

Lambda     K      H
    1.33    0.621     1.12

Gapped
Lambda     K      H
    1.33    0.621     1.12


Matrix: blastn matrix:1 -2
Gap Penalties: Existence: 5, Extension: 2
Number of Hits to DB: 3
Number of Sequences: 0
Number of extensions: 3
Number of successful extensions: 2
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Number of sequences better than 10.0: 1
Number of HSP's better than 10.0 without gapping: 1
Number of HSP's successfully gapped in prelim test: 0
Number of HSP's that attempted gapping in prelim test: 0
Number of HSP's gapped (non-prelim): 2
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length of database: 8,097,511,182
effective HSP length: 24
effective length of query: 573
effective length of database: 8,097,511,158
effective search space: 4639873893534
effective search space used: 4639873893534
T: 0
A: 0
X1: 6 (11.5 bits)
X2: 26 (50.0 bits)
S1: 12 (23.8 bits)
S2: 20 (39.1 bits)
```